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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,525	02/05/2002	Karla Robotti	10011206	2898

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/072,525	ROBOTTI, KARLA	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9,15-21,24,26-56,58 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 9, 15-21, 24, 26-56 and 58-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 3/13/07 was entered.

Amended claims 1-3, 9, 15-21, 24, 26-56 and 58-59 are pending in the present application, and they are examined on the merits herein.

Response to Arguments

The rejection under 35 U.S.C. 102(b) as being anticipated by Lochhead et al. (US 6,039,897) was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 103(a) as being unpatentable over Dunn et al. (U.S. Patent No. 5,200,334) in view of Reetz et al. (Biotechnology and Bioengineering, Vol. 9:527-534, 1996) and Lochhead et al. (US 6,039,897) was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 103(a) as being unpatentable over Lochhead et al. (US 6,039,897) in view of Avnir et al. (U.S. Patent No. 5,300,564; IDS) and Swedberg et al. (U.S. Patent No. 6,240,790) was withdrawn in light of Applicant's amendment.

Claim Objections

Claim 43 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because in claim

43 which is dependent on claim 1, the sol-gel particle size is from about 1 nm to about 30 nm which is outside the range of 10 um to about 80 um in claim 1.

Claim 55 is objected to because of the phrase "The method of claims 44 or 45", which is not grammatically correct. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended claims 45 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

In amended claim 45 and its dependent claim 55, it is unclear what is encompassed by the phrases "said sol-gel is selected from the group consisting of a monolithic gel, thin film, and fiber and wherein the sol gel is placed in or on the microanalytical device" and "the sol-gel is formed in situ on the microanalytical device", respectively. This is because in claim 44 from which both claims 45 and 55 are dependent on, crushed so-gel particulates having a diameter of from about 10 um to about 80 um, and not any other forms, were placed into a bed within the microanalytical device or on the surface of a microanalytical device. Therefore, the metes and bounds of the claim are not clearly determined or exactly what Applicant intends to claim so that the prior art could be applied.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended claims 1-3, 24, 26-27, 33-36, 41-44, 46-55 and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn et al. (U.S. Patent 5,200,334; IDS) in view of Lochhead et al. (US 6,039,897), Avnir et al. (U.S. Patent 5,300,564; IDS), Avnir et al. (US 6,159,453), and Swedberg et al. (U.S. Patent 6,240,790). ***This is a new ground of rejection.***

Dunn et al. teaches a process for the production of a porous, transparent sol-gel glass containing an alcohol sensitive active biological material entrapped therein comprising: (a) forming a single phase sol by mixing a metal alkoxide in a non-alcoholic medium comprising water and an acid catalyst in a container exposed to ultrasonic energy, the mixture having a pH not greater than about 2; (b) removing the ultrasonic energy and raising the pH of the sol to about 5 to 7 by the addition of a buffering agent; (c) adding an alcohol sensitive active biological material to the buffered sol; (d) forming a gel and allowing the gel to age; and (e) allowing at least a portion of the water in the gel to evaporate so that the volume of the product produced in step (d) is decreased and the active biological material is trapped in a monolith of the gel having a reduced

volume (see abstract, Fig. 1 and claim 1). Although exemplified method utilizes tetramethylorthosilicate (TMOS), and proteins (e.g., RNase A, proteases, hemoglobin, cytochrome c, metal ion binders, see col. 3, lines 38-59 and Table 1) as active biological materials, however other silicon alkoxides such as tetraethylorthosilicate (TEOS) and other active silicon compounds as well as other metal alkoxides (not limited to aluminium, titanium, zirconium, vanadium, sodium, calcium and boron or combinations thereof can be used (col. 2, line 60 continues to line 10 of col. 3). In an exemplified method, the gel is allowed to age at room temperature for 7 to 21 days (col. 5, lines 2-8, 17-19). The porous, transparent sol-gel glass has a median pore radius of about 15 Angstroms (1.5 nm) and a maximum pore radius of about 100 Angstroms or 10 nm (see Fig. 2, claim 22), and in the form of thin films as small as 1000 Angstroms thick or shaped gels having dimensions in its smallest direction of at least 0.5 cm or a monolith (see Summary and col. 2, lines 1-5). Dunn et al. further teaches that **encapsulated or entrapped enzymes are used with increasing frequency as micro-catalysts and analytical devices of very high sensitivity, and that enzymes have been enclosed in membranes systems and used as high-sensitivity monitoring devices. However, such membrane systems are cumbersome and difficult to miniaturize. Therefore, it would be highly advantageous to encapsulate enzymes in a porous, transparent glass structure, such as structures prepared by the sol-gel process. Such an encapsulation would be significantly easier to miniaturize and would be far less cumbersome and far more reliable than membrane encapsulating systems** (col. 1, lines 27-36). Additionally, enzyme encapsulation within a transparent

glass structure would allow for the monitoring of many enzymatic reactions by using simple, photometric monitoring systems (col. 1, lines 27-36). Because of the light transmission characteristics of the glasses, UV, IR and visible light optical spectroscopy as well as fluorescence, luminescence, absorption, emission and reflection techniques are all suitable for quantitative and/or qualitative monitoring of chemical changes produced by the sol-gel glasses with entrapped enzymes (col. 4, lines 49-56).

Dunn et al. does not teach explicitly a method of preparing any microanalytical device containing sol-gel particulates comprising an entrapped biological molecule and having a diameter of from about 10 micrometers to about 80 micrometers, or a method of using the same microanalytical device.

However, at the filing date of the present application, Lochhead et al already disclosed a Micro-molding in capillaries (MIMIC) process for **fabricating micronscale structures or devices for use in sensor, waveguide and integrated optics applications using a micro-molding fluid that is a sol that can comprise a variety of biologically active molecules including proteins, enzymes, antibodies, antigens and nucleic acid which bind to, or interact with analytes including other biologically active molecules** (see at least col. 6, lines 9-62). Lochhead et al further taught an exemplified fluid channel that is an element of a micro-fluidic chemical analysis system with appropriate means for fluid sample introduction and a means for detecting indicator response to a particular analyte that may be present in fluid passed through the micro channel (see Fig. 5, and col. 9, lines 37-62). The channel is optically accessible through an optically transparent cover for detection of dye fluorescence (col.

9, lines 37-62). Due to the presence of multiple fluid channels, the micro-fabricated devices of Lochhead et al. are capable of performing high throughput screening of samples. Additionally, the arrangement of multiple independent fluid channels in a microfabricated device can also be considered to be a form of a microarray (see Fig. 1). It is also noted that the term "monolith" means a solid-like body in one piece, and may be from several um in size to greater than tens of mm in size and beyond (page 10, lines 27-28). Lochhead et al further teaches that the potential for rapid analysis and portability makes microfabricated devices attractive for applications ranging from remote chemical sensing to medical diagnostics (col. 1, lines 18-22).

Avnir et al. (U.S. Patent 5,300,564) also taught obtaining a chemical interaction between at least one reagent trapped in sol-gel glass by doping it with the reagent, and diffusible solutes or components in an adjacent liquid or gas phase. The reagents, the solutes and the components can be any organic or inorganic compounds or materials of biological origin including enzymes (see abstract). Avnir et al. further taught that the doped sol-gel glass can be in any shape suitable for the test, for example, it can have the shape of rods, discs, cubes, sieves, **powder** or thin films coating conventional glass plates or any other inert solid support (col. 3, lines 20-24). **Avnir et al. also taught that the doped sol gel glasses can be used for all chromatographic purposes including liquid, gas and thin layer chromatography. The extraction or separation is performed by passing the solution through columns made from appropriately doped sol gel material** (col. 3, lines 445-52). **Particularly, Avnir et al. taught that for sol-gel immobilized enzymes, crushed powder sol gel glasses may be used as**

support for enzymatic column chromatography (col.5, lines 37-39, and col. 7, lines 55-57).

Avnir et al. (US 6,159,453) also taught that **doped sol-gel particulates or powder in any shape with 0.01-100 microns in diameter** were successfully made for delivering sunscreen molecules (see at least the abstract; col. 2, lines 53-62; col. 4, lines 42-47; col. 6, lines 28-32).

Furthermore, Swedberg et al also taught a high-throughput microanalysis device having a plurality of sample processing compartments for use in analysis of small and/or macromolecular and/or other solutes in the liquid phase (see abstract). The microstructures in the microanalysis device include sample separation means that include electochromatographic separations performed in columns or microcapillary format (col. 6, line 61 continues to lines 49 of col. 7). Swedberg et al further taught that the microanalysis device is interfaced with any analytical detection means well known in the art, such as UV/Vis, Near IR, fluorescence, refractive index (RI), Raman techniques, as well as Mass spectrometry (MS) and NMR well suited to yielding high quality chemical information for multi-component samples, requiring no a priori knowledge of the constituents (col. 6, lines 3-11).

Accordingly, at the effective filing date of the present application, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings for Dunn et al. by forming a micro-analytical device containing their biological material doped sol-gel particulates or powder having a diameter of about 10 microns to about 80 microns and using such micro-analytical device for **use in sensor, waveguide and integrated**

optics applications and/or analysis of small and/or macromolecular and/or other solutes in the liquid phase in light of the overall teachings of Lochhead et al., Avnir et al. (U.S. Patent 5,300,564), Avnir et al. (US 6,159,453) and Swedberg et al.

An ordinary skilled artisan would have been motivated to carry out the above modification for at least the following reasons: Dunn et al. already taught that encapsulated biological material (e.g., enzymes) prepared by the sol-gel process is easier to miniaturize and less cumbersome for use in analytical devices of very high sensitivity; Lochhead et al. already taught the feasibility of fabricating micron-scale devices containing a biological material embedded in a sol-gel at least for sensor, waveguide and integrated optics applications, and microfabriated devices are attractive for applications ranging from remote chemical sensing to medical analysis due to the potential of rapid analysis and portability; Avnir et al already disclosed that doped sol gel glasses for all chromatographic purposes including liquid, gas and thin layer chromatography and doped sol-gel particulates or powder in any shape with 0.01-100 microns in diameter were successfully made and used, and finally Swedberg et al also taught a format of a microdevice containing sample separation means that include electrochromatographic separations performed in columns or microcapillary format that allows high throughput sample processing and analysis of small and/or macromolecular solutes in biological liquids in a truly integrated fashion. In summary, an ordinary skilled artisan would have been motivated to carry out the above modification because the reduction in size of an analytical procedure of technique translates to a reduction in analysis time, costs and paves the way for high-throughput applications.

An ordinary skilled artisan would have a reasonable expectation of success based on the teachings of Dunn et al., Lochhead et al., Avnir et al. (U.S. Patent 5,300,564), Avnir et al. (US 6,159,453) and Swedberg et al., as well a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claims 1, 9, 15-21, 28-32, 37-40 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn et al. (U.S. Patent 5,200,334; IDS) in view of Lochhead et al. (US 6,039,897), Avnir et al. (U.S. Patent 5,300,564; IDS), Avnir et al. (US 6,159,453), and Swedberg et al. (U.S. Patent 6,240,790) as applied to claims 1-3, 24, 26-27, 33-36, 41-44, 46-55 and 58-59 above, and further in view of Liu et al (US 6,303,290; IDS) and Reetz et al. (Biotechnology and Bioengineering, Vol. 9:527-534, 1996). ***This is a new ground of rejection.***

The teachings of Dunn et al., Lochhead et al., Avnir et al (US 5,300,564), Avnir et al (US 6,159,453) and Swedberg et al have been discussed above. <u>However, none of the references teaches specifically the making of a porous, inorganic matrix containing a biological material encapsulated therein comprised of colloidal silica sol and dissolved sodium silicate or a tetralkyl orthosilicate and a substituted silane as recited</u>.

However, at the effective filing date of the present application, Liu et al already taught an alcohol-free method of making a porous, inorganic matrix containing a biological material (e.g., RNA, DNA, active proteins, active fragments of DNA, RNA,

proteins, enzymes such as RNase, DNase, nuclease, kinase, transferase, trypsin, chymotrypsin, cytochrome c (MW of 12,327) encapsulated therein comprised of colloidal silica sol and dissolved sodium silicate suitable for quantitative or qualitative detection of a test substance that reacts with or whose reaction is catalyzed by an active biological material (col. 3, lines 47-67; col. 4, lines 1-28; col. 4, line 62 continues to line 17 of col. 5). Liu et al further taught that unlike the conventional silica-based, metal alkoxide methods, the types of biopolymers that can be incorporated in the porous, inorganic matrix composites are essentially unlimited due to the completely elimination of alcohol in the process of making (col. 3, lines 34-45).

Additionally, Reetz et al. also taught that lipase activity for lipases entrapped in sol-gels prepared from a mixture of tetramethoxysilane (TMOS) and alkyltrimethoxysilanes $Rsi(OCH_3)_3$ **was dramatically enhanced** with increasing amount and alkyl chain length of the hydrophobic silanes, including the alkyl group C_{18} (page 529, right-handed column, first complete paragraph and Figure 1).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the method taught by Dunn et al., Lochhead et al., Avnir et al (US 5,300,564), Avnir et al (US 6,159,453) and Swedberg et al by using a sodium silicate or a substituted silane in the process of immobilizing an enzyme, particularly a lipase, or other biological material in a sol-gel containing colloidal silica sol, in light of the above teachings of Liu et al., and Reetz et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because of the advantages offered by a porous, inorganic matrix

composites comprised of colloidal silica sol and dissolved sodium silicate taught by Liu et al., namely essentially unlimited types of biopolymers can be incorporated and that the denaturation of many biopolymers can be avoided due to the completely elimination of alcohol in the process of making. Additionally, Reetz et al. taught that increasing amount and alkyl chain length of the hydrophobic silanes, including the alkyl group C_{18} enhance the activity and/or stability at least for lipase-doped sol-gel.

An ordinary skilled artisan would have a reasonable expectation of success based on the teachings of Dunn et al., Lochhead et al., Avnir et al (US 5,300,564), Avnir et al (US 6,159,453), Swedberg et al, Liu et al., and Reetz et al., as well a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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PRIMARY EXAMINER